LETTERS

Effect of Different Pharmacological Formulations of Gliclazide on Postprandial Hyperglycaemia

The pharmaceutical preparation of sulphonylurea tablets can affect their pharmacokinetics.[1] It has been recently reported that two different formulations of gliclazide may have a different dissolution kinetics.[2] We have compared two formulations: formulation A (Diamicron™, Laboratories Servier, Gidy, France) containing gliclazide 80 mg, lactose 66.3 mg, polyvinilpyrolidone (PVP) 8 mg, glyceril-behenate 5 mg, magnesium stearate 0.4 mg, colloidal silex 0.3 mg; formulation B (Diabrezide™, Molteni Farmaceutici, Florence, Italy) containing gliclazide 80 mg, lactose 33 mg, microcrystallin cellulose 20 mg, PVP 16 mg, sodium amylum glycolate 8 mg, magnesium stearate 3 mg.

The study was performed on eight volunteers (6 males, 2 females), with Type 2 diabetes mellitus, aged (mean ± SD) 58.7 ± 9.3 years, duration of diabetes of 7.4 ± 7.6 years, HbA_{1c} 6.0 ± 1.2 %, and body mass index 29.9 ± 4.9 kg m^{-2}, who had not received any pharmacological treatment in the previous 4 weeks. All participants gave their informed consent prior to the beginning of the study.

On the first day of the study, at 8.00 am, after overnight fast, two samples of venous blood were drawn at an interval of 15 min, to evaluate fasting glucose, insulin, and serum C-peptide levels; the means of the two measurements were used as baselines. Patients then randomly received formulation A or B. The patient was unaware of the treatment assigned, which was known to the physician. Ten minutes later, patients ate 25 g of white bread, together with coffee, and 50 g of skimmed milk and artificial sweetener (Aspartame) to taste. Blood was sampled at 60, 120, and 240 min. Patients were re-studied on the alternate formulation 7 days later and after a further 7 days, without any pharmacological treatment. Serum insulin was measured with an immunoassay (Boehringer Mannheim, Tutzing, Germany); serum C-peptide was evaluated through radioimmunoassay (Biodata Diagnostics, Rome, Italy).

Baseline plasma glucose (see Figure 1) was not significantly different prior to the three treatments. The AUC of plasma glucose was 32.7 ± 7.2 mmol l^{-1}/2h with formulation A, 26.4 ± 6.9 with formulation B, and 34.1 ± 8.7 in control ($p < 0.05$ by ANOVA). The glucose AUC after formulation B was significantly lower than with formulation A or control ($p < 0.05$ at paired Student's *t*-test), there were no significant differences between formulation A and control. No significant differences between the three treatments were observed in AUC of insulin and C-peptide (data not shown).

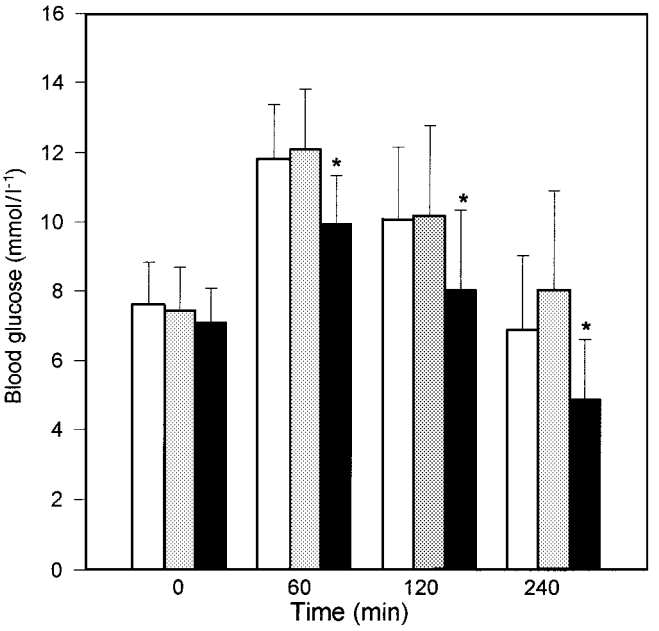

Figure 1. Glycaemic profile (mean ± SD) after formulation A (grey bars), formulation B (black bars), and in control conditions (white bars); *$p < 0.01$

Previous reports show that formulations of gliclazide containing glyceril-behenate may have a slow dissolution pattern *in vitro* at pH 7.4 and 1.2; while formulations containing sodium amylum glycolate seemed to show more rapid dissolution in aqueous solutions.[2] Such kinetic differences might lead to a difference in the bioavailability, and therefore in efficacy, of different formulations of gliclazide. Indeed, in controlled conditions, such as those of the present study, formulation B (containing sodium amylum glycolate) does appear to induce a greater reduction of postprandial blood glucose levels than formulation A (which contains glyceril-behenate). This might affect control of early postprandial hyperglycaemia.

This is the first study of *in vivo* pharmacokinetics of two formulations of gliclazide and further pharmacokinetics studies, especially *in vivo* studies on drug bioavailaility, are urgently needed. It should be noted that a difference in the acute effects on postprandial hyperglycaemia in controlled conditions does not necessarily imply that a similar difference can be observed on long-term metabolic control; this should be assessed through medium-term controlled trials.

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Right Lateral Position Reduces Intra-individual Variation during Oral Glucose Tolerance Tests

A rise in plasma glucose levels after glucose ingestion correlates with gastric emptying rate (GER).[1,2] In the oral glucose tolerance test (OGTT), the time–concentration profile during the first 30 min greatly depends on GER, and that during the later phase primarily represents the effect of insulin.[3] This suggests that OGTTs will become a more direct reflection of glucose intolerance if an intra-individual variability in GER during the first 30 min can be minimized. A previous study has shown that a consistent acceleration of GER by a prokinetic drug makes OGTTs reproducible, probably because of the reduction in intra-individual variation in GER.[4] A simpler manoeuvre for enhancing GER is to place the subject in the right lateral decubitus position, in which the pylorus is at the 'bottom' of the stomach.[5] We investigated the influence of the right

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Table 1. Intra-individual variabilities in results of the standard and modified oral glucose tolerance tests during the first 30 min

Subject	Age (years)	Body mass index (kg m^{-2})	CV 15 (%)[a]		CV 30 (%)[b]	
			Standard	Modified	Standard	Modified
A	31	26.0	43.2	16.2	24.7	14.6
B	29	23.9	46.5	27.4	22.1	18.0
C	24	21.7	40.3	25.0	23.2	19.6

[a]CV 15, coefficients of variation for differences in plasma glucose concentrations between 0 and 15 min.
[b]CV 30, coefficients of variation for differences in plasma glucose concentrations between 0 and 30 min.

lateral decubitus on the intra-individual variability in OGTTs.

Three healthy male volunteers were studied. After overnight fast, each underwent the five standard and the five modified OGTTs within 2 months. Immediately after obtaining fasting blood samples (0 min), 200 ml water containing 75 g glucose was consumed in a sitting position. Consecutive blood samples were obtained at 15, 30, and 60 min. In the standard OGTTs, the sitting position was maintained throughout the tests. In the modified OGTTs, the volunteers kept themselves in the sitting position from 0 to 5 min to prevent the gastro-oesophageal reflux, moved into the right lateral position from 5 to 30 min, and resumed the sitting position thereafter. The intra-individual variation was expressed as a coefficient of variation for difference in plasma glucose concentrations between 0 and 15 min (Δ 15) and that between 0 and 30 min (Δ 30). In addition, Δ 15 and Δ 30 were compared between the standard and the modified OGTTs in every subject by the Mann–Whitney test.

Table 1 shows that the intra-individual variabilities during the first 30 min were smaller in the modified than in the standard OGTTs. Figure 1 demonstrates the most representative time–concentration curves. However, the differences in Δ 15 and Δ 30 were not significant ($p > 0.05$) in all subjects, suggesting that the right lateral decubitus did not necessarily promote the rate of glucose absorption.

In the sitting position, plasma glucose levels in the early course of OGTTs become unexpectedly high (low) when the timing of glucose ingestion incidentally meets the active (quiescent) phase of gastric motility.[4,6] Thereby, the time-course of the standard OGTTs during the early phase can vary considerably. In the right lateral position, on the other hand, GER is governed by gravity regardless of the phase of gastric motility.[5] Indeed, the rate of glucose absorption may not always be hastened, but the gravity-dependent GER is considered more constant. This is the likely explanation for the reduced variabilities in the modified OGTTs. The modified OGTT may be more sensitive in the diagnosis of impaired glucose tolerance, but further studies are required regarding its clinical usefulness.

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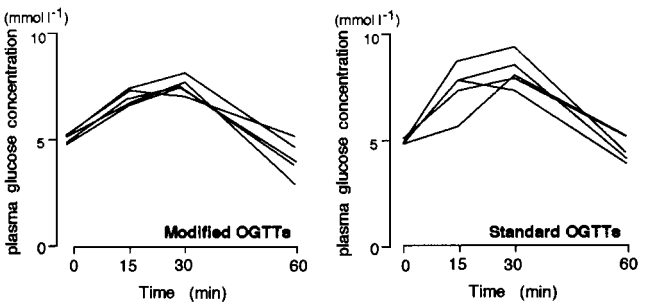

Figure 1. The most representative time–glucose concentration profiles in the modified and standard oral glucose tolerance test (OGTT) in subject A. A smaller intra-individual variation from 0 to 30 min is noted in the modified than in the standard OGTTs

Commercially Sponsored Supplements

In a recent letter,[1] Dr Michael Berger was critical of the publication of 'commercially sponsored supplements' to *Diabetic Medicine*. His letter was prompted by a Bayer-sponsored supplement on the postprandial state and the risk of atherosclerosis and included direct criticism of our contribution to that supplement. Dr Berger's criticism was that we considered the use of acarbose and glibenclamide for the treatment of Type 2 diabetes 'without relationship to the title' of the supplement. Acarbose, an alpha-glucosidase inhibitor inhibits the release of glucose from oligo- and complex carbohydrates in the small intestine[2] and so reduces postprandial hyperglycaemia,[3] postprandial hyperinsulinaemia,[3,4] postprandial hypertriglyceridaemia[4] and postprandial coagulation activation.[5] Thus, acarbose is a prominent candidate to correct abnormalities in the postprandial phase in Type 2 diabetic subjects. Dr Berger expresses concern about 'the lack of any meaningful lowering of HbA_{1c} in a properly controlled trial as the UKPDS'. There are, however, numerous publications of carefully controlled trials[3,4,6,7] that prove the efficacy and safety of acarbose in long-term trials. In Holman's publication, to which he refers,[8] acarbose reduced HbA_{1c} by 0.7 % which is in the same range as with glibenclamide and insulin in the UKPDS.[9] With respect to safety Dr Berger refers to a statement from a conference he organized to scrutinize efficacy and safety

